REMARKS

Status of the Claims

Claims 101-112 were pending.

Claims 101-112 stand rejected.

Claims 101 and 111 are amended.

Claims 112-130 are new claims.

Reconsideration is respectfully requested.

It is gratefully acknowledged that the PTO has reopened prosecution in view of the appeal brief filed July 21, 2004, and entered claims 101-112. Below, applicant will discuss the new claims and claim amendments presented herein, and then respond to the rejections stated in the Office Action.

I. Discussion of New and Amended Claims

Claims 113 through 116 are new dependent claims, depending upon claims 101 and 107 (which also depends on claim 101). Claims 113 and 114 add the limitation that the cancer being treated is resistant, refractory, or sensitive to taxane treatment, which is supported in the specification, inter alia, at pages 54-56. Claims 115 and 116 add the limitation that the Compound (1) ("ixabepilone") is administered orally which is supported, inter alia, at page 21, lines 12-18, page 37, and page 65, lines 1-2.

New independent claims 117 and 126 are directed to treating particular cancers selected from metastatic breast cancer, lung cancer, pancreatic cancer, ovarian cancer, prostate cancer, colon cancer, and/or small cell lung cancer, via the combination of capecitabine (and/or in claim 126, 5-FU) and Compound (1). The particular cancers recited in these claims are supported at page 26, lines 1-4, and page 25, line 10-19 of the specification. New claim 117 states that the combined "administration will provide a greater anti-cancer effect than the effect obtainable with either the dosage unit of capecitabine or the dosage unit of Compound (1) alone," and new claim 126 recites the same concept in an alternative way, *e.g.*, using the term "synergistic effect." These claims are supported throughout the specification, including without limitation at pages 8, lines 26-31, page 20, page 22, lines 4-9, and pages 40-42. It is noted that the specification throughout makes

reference to applicant's discovery of a synergistic effect (*see, e.g.*, page 2, line 32, page 9, line 8, page 43, line 10, and so forth).

New claims 118 to 125 and 127 to130 are dependent upon new claims 117 and 126, respectively, and add the limitations that the cancer being treated is breast cancer, and/or resistant, refractory, or sensitive to taxane treatment, and/or recite the timing or mode of administration, which are supported in the specification, inter alia, at pages 25-26, page 44, lines 10-25, pages 54-56, and page 65, lines 1-2.

Claims 101 and 111 are amended to refer to alternate forms of Compound (1), which are supported, for example, at page 4, lines 24-26, and page 20. Pages 35-36 describe various salt forms of Compound (1). Claim 101 also is amended to recite that the cancer being treated is selected from particularly-named cancers which are described at pages 25-26 of the specification.

Response to Office Action

Claims 101-112 stand rejected under Section112 (enablement), Section 103 (obviousness), and for alleged obvious-type double patenting in view of US Pats. 6,686,380 and 6,605,599, assigned to the present assignee. Applicant traverses these rejections for the reasons below.

Section 112 Rejections

Claims 101-112 stand rejected under Section112 on the ground that the specification does not reasonably provide enablement for **any** cancers.

It is gratefully acknowledged the Office Action concedes the specification is "enabling for treating specific cancers or tumors in the specification." (Page 3). In this respect, applicant submits the Section 112 rejection should not have been applied to all claims. Claims 107, 108, 109 and 110 recite specific cancers described in the specification, *i.e.*, metastatic breast cancer, lung cancer, pancreatic cancer, and prostate cancer. (See page 26, lines 1-4, and page 25, line 10-19 of the specification.) Thus, the Section 112 rejections should not have been applied to these claims. Applicant respectfully requests that each claim be evaluated independently.

Regarding the remaining claims, applicant traverses the enablement rejection. Applicant submits that following *In re Brana*, 34 USPQ2d 1436, 1441 n. 16 (Fed. Cir. 1995), it is now well accepted that a claim to treating "cancer" generally should not be rejected under Section 112, absent a showing by the Examiner, preferably based on documentary evidence, that the treatment of cancer with the claimed compounds presents an inherently unbelievable undertaking. *In re Brana*, 34 USPQ2d at 1434 (""The purpose of treating cancer with chemical compounds *does not suggest an inherently unbelievable undertaking* or involve implausible scientific principles. . . . Modern science has previously identified numerous successful chemotherapeutic agents"). MPEP § 2107.01(b) and MPEP 2107.01(c).

Additionally, the enablement requirement is satisfied where the specification teaches one skilled in the field how to make and use the invention without undue experimentation. *PPG Indus. Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The rule should not be applied in a way that discourages the early filing of applications. *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981) ("Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public"). One skilled in the field may determine without undue experimentation other potential types of cancer not recited in the specification, whether the cancers may be effectively treated with the claimed combination, the appropriate dosages for the treatment, and so forth.

However, in order to expedite prosecution and without waiver of this traversal, claim 101 has been amended to recite that the cancer being treated is one selected from cancers that are specifically recited in the specification at pages 25-26. Since the Examiner has stated that the claims are "enabling for treating specific cancers or tumors in the specification" (Office Action, Page 3), it is believed this amendment should obviate the Section 112 rejection. Accordingly, it is respectfully requested that the Section 112 rejection be withdrawn.

Section 103

Each of the claims herein is directed to a method of administering a combination, or a pharmaceutical product involving a combination, of Compound 1 (also now known as "ixabepilone"), and an anti-metabolite selected from capecitabine and/or 5-fluorouracil.

The claims stand rejected under 35 USC § 103(a) as being obvious over Vite *et al.*, WO 99/02514 (corresponding with US Pat. 6,605,599 B1), in view of The Merck Index (12th Ed, 1996 ("Merck Index"), and Miwa et al., European Journal of Cancer (1998), 34(8), 1274-81 ("Miwa"). It is argued that according to the Merck Index, it is known that 5-FU can be combined with other anti-cancer agents such as doxorubicin, cyclophosphamide, mitomycin C, methotrexate, cisplatin, epirubicin, carmustine, vinblastine, and so forth. It is further argued that based on Miwa, one would be motivated to replace 5-FU with capecitabine, and thus, allegedly based on this information it would be obvious to combine capectiabine with ixabepilone (Compound (1)), as the composition-of-matter patent for ixabepilone (Vite *et al.*) states that the compound may potentially be used in combination with other chemotherapeutic agents.

This argument clearly reflects an impermissible picking and choosing to reconstruction the applicant's invention based on the instant disclosure. The reliance now placed upon the Merck Index, considering the thousands of compounds and combinations listed therein, to select from that reference an entry relating to various other combinations with 5-FU, underscores that the USPTO is not engaging in a proper obviousness analysis. *See Smithkline Diagnostic Inc. v. Helena Labs Corp.,* 859 F.2d 878, 887, 8 USPQ2d 1468 (Fed. Cir. 1988) ("[i]t is inappropriate to "pick and choose ... elements of assorted prior art references to recreate the claimed invention").

In considering a conclusion of obviousness, the Federal Circuit has established three essential standards for the USPTO to meet, as a minimum, thus guarding against the application of hindsight and inconsistent decisions. Specifically, a *prima facie* case of obviousness requires findings that: (1) the prior art contains *a suggestion or motivation* for modifying or combining the references; (2) the proposed modifications have a reasonable expectation of success in the prior art; and (3) the references teach or suggest *all* claim limitations. *See In re Chu*, 66 F.3d 292, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995); *In re*

Oetiker, 977 F.2d 1443, 24 USPQ2d 1443, 1444-46 (Fed. Cir. 1992); and MPEP § 2143. The burden of satisfying these requirements rests with the PTO. *See Ex Parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. & Inter. 1986); MPEP § 2142.

Here, the three-part test expressed in *In re Chu* and MPEP § 2143 has not been applied. The by-passing of this test raises the concerns for hindsight reconstruction of the invention. *See In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("rigorous application" of the obviousness standards is required to guard against the "subtle but powerful attraction of a hindsight-based obviousness analysis.") Of all the thousands of compounds and combinations listed in The Merck Index, the references to combinations with 5-FU have been picked to provide a reference that can be used to recreate the claimed invention. However, there is no motivation in the prior art for selecting out of the Merck Index, the various entries to 5-FU, and/or for modifying or combining the cited references.

The Office Action argues a motivation for combining the references exists because both Vite *et al.*, and the Merck Index, suggest generally that combinations of agents involving either of the two agents separately and/or others may be useful. However, this argument proves too much. The fact that references can be combined does not render the resultant combination obvious, unless there is a suggestion *in the prior art* for *making* the combination. MPEP § 2143.01.

Additionally, there is no basis in the prior art for concluding the proposed modifications would have a reasonable expectation of success, and further, the references do not teach or suggest *all* claim limitations. The Office Action argues at page 8 that one of ordinary skill in the field would have reasonably expected that the claimed combination would improve effects with the agents and/or produce additive therapeutic benefits. However, this is a conclusory statement, unsupported by any actual evidence or references in the prior art. The absence of any actual evidence to support this statement makes clear that reliance is being placed upon applicant's disclosure. However, the reasonable expectation of success of the invention must be found in the prior art, not in applicant's

disclosure. *In re Dow Chem.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) ("Both the suggestion and the expectation of success must be founded in the prior art").

That the reasoning set forth in the Office Action is insufficient to support an obviousness conclusion is underscored by the Federal Circuit's recent decision in *Knoll v. Teva Pharm. USA*, 367 F.3d 1381 (Fed. Cir. 2004). In this case, a patent was granted to Knoll Pharmaceuticals for a method of treating pain with a claimed combination of hydrocodone (a/k/a Vicoden®) and ibuprofen. The method claims recited that the combination provided a greater analgesic effect than either agent alone, and composition claims were also granted that did not contain the limitations regarding these effects. *Id.* at 1383. There was evidence in the case that the prior art had taught combining an opiod, such as hydrocodone, with various NSAIDs, such as ibuprofen. *Id.* at 1384. On this evidence, the district court had entered summary judgment, finding the claimed combination obvious. However, the Federal Circuit reversed because there was no "evidence of prior art teaching or suggesting the enhanced biomedical effect of the combination of hydrocodone and ibuprofen." *Id.* The court further concluded that evidence of this enhanced effect should have been considered, even if the evidence was gathered after the patent was granted. *Id.* at 1385.

Here, there is no evidence of prior art teaching of obtaining an improved effect with the claimed combination. In this respect, the applicant draws the Examiner's attention to Exhibit A herewith, reflecting preclinical test results wherein the combined efficacy of ixabepilone and capecitabine was evaluated alongside ixabepilone and capecitabine administered as single agents. A xenograft model was used, in which tumor cells, specifically of the human colon carcinoma cell line GEO, were transplanted into mice, the drugs were administered to the mice, and tumor responses were measured. Each symbol represents the median tumor burden of a group of 8 mice. (●) control; (□) capecitabine, 250 mg/kg/adm, QD x 10, PO; (▲) ixabepilone, 10 mg/kg/adm, Q4D x 3, IV; (◇) capecitabine, 250 mg/kg/adm, QD x 10, PO + , ixabepilone 10 mg/kg/adm, Q4D x 3, IV , wherein QD = every day and PO = orally. As can be seen, the mice administered the combination of ixabepilone and capecitabine had an improved response as measured by tumor weight/growth for a greater period of time as compared with when ixabepilone or

capecitabine were administered as single agents. Phase III clinical trials comprising administration to humans of a combination therapy of ixabepilone and capecitabine are underway and now on-going.

For the foregoing reasons, a *prima facie* obviousness case has not been established, and it is respectfully requested that the Section 103(a) rejection be withdrawn.

Obviousness-type double patenting

Claims 101 to 112 also stand rejected on grounds of obviousness-type double patenting in view of US Pat. 6,686,380 and 6,605,599, assigned to the present assignee.

In particular, reliance is placed upon claim 12 of the '380 patent and claims 33-34 and 57-58 of the '599 patent which generally recite combinations of ixabepilone with other chemotherapeutic agents. This argument stands or falls with the above rejection under Section 103. Applicant thus raises the same traversal as set forth above. Regarding the reference to pyrimidine analogs, applicant notes that in *Knoll v. Teva Pharm. USA, supra,* there was evidence in the prior art teaching a combination of an opiod, such as hydrocodone, with various NSAIDs, such as ibuprofen, but the obviousness ruling was reversed as there was no evidence teaching an enhanced effect with the claimed combination. Lastly, the Office Action states that "the instant claims 101-112 are seen to anticipate claim 12 of U.S. Patent 6,686,380." However, the instant claims are not prior art to the '380 patent. Whether or not the instant claims may anticipate earlier claims of a co-pending patent does not support an obviousness-type double patenting rejection in this case.

IDS

Applicant brings to the Examiner's attention that an IDS is submitted herewith. The IDS includes many references previously listed on a form 1449 that apparently were not considered (they were crossed off the 1449) on the grounds that the references were not supplied and/or were improperly cited. Also provided with the IDS are various co-pending patents and/or patent applications or documents related to ixabepilone and assigned to the present assignee.

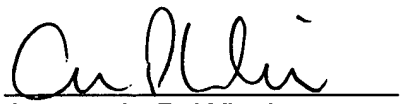
FEES

Applicant has added seventeen new claims including two independent claims. However, applicant had previously paid fees for up to 100 claims and the application now contains just twenty-nine claims. Thus, is it believed no fee is due. However, in the event it is determined a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb.

SUMMARY

It is believed that all rejections of the claims have been fully addressed and that the instant claims are in condition for allowance. The Examiner is invited to contact the undersigned if it is believed a telephonic communication would expedite the prosecution of this application.

Respectfully submitted,



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